CLINICAL PRIORITIES ADVISORY GROUP
6 October 2021

Agenda Item No	2.2
National Programme	Internal Medicine
Clinical Reference Group	Specialised Rheumatology
URN	1925

Title
Abatacept for refractory idiopathic inflammatory myopathies (adults and children aged 2 years and over)

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its approval as an IYSD

Proposition
For routine commissioning: The proposition is for Abatacept to be routinely commissioned as a third-line treatment for refractory idiopathic inflammatory myopathies (IIMs) in adults and children aged 2 years and above within the criteria set out in the policy. There are some reductions in cost through transitioning from the use of intravenous immunoglobulin (IVIg) as a treatment which is one of the current treatments for IIMs.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report and an additional evidence report.
2.	The Head of Acute Programmes confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.

4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

In the Population what is the clinical effectiveness and safety of the Intervention compared with Comparator?

Outcome	**Evidence statement**
Clinical Effectiveness	
Critical outcomes	
Total improvement score **Certainty of evidence:** Moderate and low	Total improvement score is a composite measure[a] and is relevant to patients because it provides an overview of their improvement across 6 core measures that can relate to functionality and quality of life. 1 study (randomised controlled trial (RCT)) provided evidence relating to total improvement score measured at 3 months. At this timepoint, the comparison was abatacept (immediate treatment group) compared to standard treatment (delayed treatment group). This study also provided evidence relating to minimum total improvement score after six months treatment with abatacept. 1 RCT (Tjärnlund et al 2018) (n=20) showed a *statistically significantly higher* median (interquartile range (IQR)) total improvement score at 3 months favouring abatacept (28.8, IQR 15 to 37.5) compared to standard treatment (5.0, IQR 0 to 12.5) (p=0.03). **(MODERATE)** At 3 months the percentage of patients achieving a minimal total improvement (≥20 points) was 60% for patients receiving abatacept and 20% for patients receiving standard treatment. Total improvement score after 6 months of abatacept was only presented graphically. However, 90% of patients in the immediate treatment group achieved a minimum total improvement after 6 months of abatacept. This was 40% in the delayed treatment group (statistical comparison between groups not reported). The study reported moderate improvement (≥40 points) for 40% of the immediate treatment group and 10% of the delayed treatment group but did not report a time period for this assessment. No patients achieved a major improvement (≥60 points). **(all LOW)**

Outcome	Evidence statement
	This study provides moderate and low certainty evidence that compared to standard treatment, abatacept does improve total improvement score at 3 months.
Muscle strength **Certainty of evidence:** Moderate and low	Muscle strength is relevant to patients because it can relate to mobility and independence and can impact quality of life. 1 study (RCT) provided evidence relating to muscle strength assessed by the Manual Muscle Test-8 (MMT-8)[b] measured at 3 months. At this timepoint, the comparison was abatacept compared to standard treatment. This study also provided evidence relating to muscle strength measured at baseline and after 6 months treatment with abatacept. 1 RCT (Tjärnlund et al 2018) (n=20) showed a *statistically significantly higher* mean difference (standard deviation (SD)) between baseline and month 3 for muscle strength favouring abatacept (2.5, SD 4.7) compared to standard treatment (-4.9, SD 9.1) (p=0.038). **(MODERATE)** There was also a *statistically significant improvement* in median (IQR) muscle strength favouring 6 months treatment with abatacept (74, IQR 68.5 to 78) compared to baseline (70, IQR 64 to 73) (p=0.047). **(LOW)** **This study provides moderate and low certainty evidence that compared to standard treatment, abatacept does improve muscle strength at 3 months and that compared to baseline, abatacept does improve muscle strength after 6 months.**
Disability/ function **Certainty of evidence:** Moderate and low	Disability/ function is relevant to patients because it can relate to independence and quality of life and identify unknown and unquantified benefits and risks of the intervention. 1 study (RCT) provided evidence relating to disability/ function assessed by Health Assessment Questionnaire (HAQ)[c] measured at 3 months. At this timepoint, the comparison was abatacept compared to standard treatment. This study also provided evidence relating to disability/ function measured at baseline and after 6 months treatment with abatacept. 1 RCT (Tjärnlund et al 2018) (n=20) showed *no statistically significant difference* in mean difference (SD) between baseline and month 3 for disability/ function for abatacept (-0.2, SD 0.4) compared to standard treatment (-0.0006, SD 0.2) (p=0.296). **(MODERATE)** There was also *no statistically significant difference* in median (IQR) disability/ function after 6 months treatment with abatacept (1.00, IQR 0.38 to 1.44) compared to baseline (1.00, IQR 0.63 to 1.81) (p=0.427). **(LOW)** **This study provides moderate and low certainty evidence that compared to standard treatment, abatacept does not improve disability/ function at 3 months and that compared to baseline, abatacept does not improve disability/ function after 6 months.**
Physician global activity score	Physician global activity score is relevant to patients because it is an assessment of disease activity and can relate to quality of life.

Outcome	Evidence statement
Certainty of evidence: Moderate and low	1 study (RCT) provided evidence relating to physician global activity score assessed by Visual Analogue Scale (VAS)[d] measured at 3 months. At this timepoint, the comparison was abatacept compared to standard treatment. This study also provided evidence relating to physician global activity score measured at baseline and after 6 months treatment with abatacept. 1 RCT (Tjärnlund et al 2018) (n=20) showed *no statistically significant difference* in mean difference (SD) between baseline and month 3 for physician global activity score for abatacept (-10.8, SD 13.7) compared to standard treatment (0.3, SD 13.8) (p=0.096). **(MODERATE)** There was also *no statistically significant difference* in median (IQR) physician global activity score after 6 months treatment with abatacept (20.0, IQR 10.0 to 40.5) compared to baseline (30.0, IQR 22.5 to 46.0) (p=0.063). **(LOW)** **This study provides moderate and low certainty evidence that compared to standard treatment, abatacept does not improve physician global activity score at 3 months and that compared to baseline, abatacept does not improve physician global activity score after 6 months.**
Patient global activity score **Certainty of evidence:** Moderate and low	Patient global activity score is relevant to patients because it is an assessment of disease activity and can relate to quality of life. 1 study (RCT) provided evidence relating to patient global activity score (assessed by VAS[d]) measured at 3 months. At this timepoint, the comparison was abatacept compared to standard treatment. This study also provided evidence relating to patient global activity score measured at baseline and after 6 months treatment with abatacept. 1 RCT (Tjärnlund et al 2018) (n=20) showed *no statistically significant difference* in mean difference (SD) between baseline and month 3 for patient global activity score for abatacept (-1.1, SD 15.8) compared to standard treatment (2.1, SD 18.5) (p=0.434). **(MODERATE)** There was also *no statistically significant difference* in median (IQR) patient global activity score after 6 months treatment with abatacept (29.0, IQR 13.5 to 69.5) compared to baseline (42.0, IQR 24.5 to 74.0) (p=0.458). **(LOW)** **This study provides moderate and low certainty evidence that compared to standard treatment, abatacept does not improve patient global activity score at 3 months and that compared to baseline, abatacept does not improve patient global activity score after 6 months.**
Muscle enzymes **Certainty of evidence:** Moderate and Low	Muscle enzymes are relevant to patients because they are an indicator of muscle injury or disease. Higher creatine kinase levels indicate muscle injury. Higher lactate dehydrogenase levels indicate tissue damage.

Outcome	Evidence statement
	1 study (RCT) provided evidence relating to muscle enzymes (microcat/litre) measured at 3 months. At this timepoint, the comparison was abatacept compared to standard treatment. This study also provided evidence relating to muscle enzymes measured at baseline and after 6 months treatment with abatacept. 1 RCT (Tjärnlund et al 2018) (n=20) showed *no statistically significant difference* in mean difference (SD) between baseline and month 3 for creatine kinase levels for abatacept (-3.2, SD 10.9) compared to standard treatment (13.5, SD 18.7) (p=0.094). There was also *no statistically significant difference* in mean difference (SD) between baseline and month 3 for lactate dehydrogenase levels for abatacept (-0.3, SD 1.3) compared to standard treatment (1.9, SD 3.3) (p=0.065). **(both MODERATE)** There was *no statistically significant difference* in median (IQR) creatine kinase levels after 6 months treatment with abatacept (2.8, IQR 1.5 to 7.1) compared to baseline (3.0, IQR 2.0 to 30.4) (p=0.438). There was also *no statistically significant difference* in median (IQR) lactate dehydrogenase levels after 6 months treatment with abatacept (4.0, IQR 3.1 to 4.6) compared to baseline (4.5, IQR 3.8 to 7.1) (p=0.299). **(both LOW)** **This study provides moderate certainty evidence that compared to standard treatment, abatacept does not improve muscle enzymes at 3 months and low certainty evidence that compared to baseline, abatacept does not improve muscle enzymes after 6 months.**
Important outcomes	
Disease activity **Certainty of evidence:** Moderate and low	Disease activity is relevant to patients because it can relate to quality of life. 1 study (RCT) provided evidence relating to disease activity (assessed by extra-muscular global assessment, VAS[d]) measured at 3 months. At this timepoint, the comparison was abatacept compared to standard treatment. This study also provided evidence relating to disease activity measured at baseline and after 6 months treatment with abatacept. 1 RCT (Tjärnlund et al 2018) (n=20) showed a *statistically significantly higher* mean difference (SD) between baseline and month 3 for disease activity favouring abatacept (-12.7, SD 14.5) compared to standard treatment (1.4, SD 12.2) (p=0.0353). **(MODERATE)** There was *no statistically significant difference* in median (IQR) disease activity after 6 months treatment with abatacept (23.0, IQR 9.0 to 36.0) compared to baseline (30.0, IQR 15.5 to 43.5) (p=0.1958). **(LOW)** **This study provides moderate certainty evidence that compared to standard treatment, abatacept does improve disease activity at 3 months. However, compared to baseline, low certainty evidence indicates abatacept does not improve disease activity after 6 months.**

Outcome	Evidence statement
Quality of life **Certainty of evidence:** Low	Quality of life is relevant to patients because it provides an indication of an individual's general health and ability to participate in and enjoy life events. Analysis from 1 study (RCT) provided evidence relating to quality of life (assessed by SF-36 physical health component[e]) measured at baseline and after 6 months treatment with abatacept. 1 study (Tjärnlund et al 2018) (n=20) showed a *statistically significant improvement* in median (IQR) quality of life favouring 6 months treatment with abatacept (37, IQR 24 to 45) compared to baseline (31, IQR 24 to 35) (p=0.005). **(LOW)** **This study provides low certainty evidence that compared to baseline, abatacept does improve quality of life after 6 months.**
Number of relapses **Certainty of evidence:** Not applicable	Number of relapses is relevant to patients because it relates to the return of the condition and can negatively impact quality of life. **No evidence was identified for this outcome.**
Safety	
Adverse events **Certainty of evidence:** low	Adverse events are relevant to patients because they can result in death or be life threatening and can result in persistent or significant disability or incapacity. They can also require hospitalisation, prolong existing hospitalisation or require additional treatment. Analysis from 1 study (RCT) provided evidence relating to adverse events after 6 months treatment with abatacept. No comparative evidence was provided for this outcome. 1 study (Tjärnlund et al 2018) (n=20) reported 8 adverse events that were considered related to treatment with abatacept. None of these adverse events were described as serious or severe. Four of the adverse events reported were moderate and four were mild. Further details for the abatacept related adverse events were not reported. **This study provides low certainty evidence that 6 months treatment with abatacept is associated with a small number of moderate or mild adverse events.**

[a] Total improvement score (0-100) is a consensus-based response score (the EULAR response criteria) that includes 6 core set measures (physician, patient and extra-muscular global activity, muscle strength, Health Assessment Questionnaire and muscle enzyme levels). Higher scores indicate more improvement. There are agreed thresholds for minimal, moderate and major improvement (Aggarwal et al 2017)
[b] The Manual Muscle Test is scored from 0 to 80 with higher scores indicating greater muscle strength
[c] The Health Assessment Questionnaire is scored from 0 to 3 with higher scores indicating greater disability

[d] Visual Analogue Scales are 0 to 100mm with higher scores indicating a higher level of disease activity
[e] The SF-36 is scored from 0 to 100 with higher scores indicating better quality of life. Only the physical health component score was reported

From the evidence selected is there any data to suggest that there are subgroups of patients with refractory IIMs that would benefit from treatment with abatacept more than others?

Outcome	Evidence statement
Subgroups	No evidence was identified regarding any subgroups of patients that would benefit more from treatment

In children and adults with refractory IIMs, what is the cost effectiveness of abatacept compared with current standard treatment?

Outcome	Evidence statement
Cost effectiveness	No evidence was identified for cost effectiveness

Patient Impact Summary

The condition has the following impacts on the patient's everyday life:

- **mobility:** Patients can have severe problems in walking about or are unable to walk
- **ability to provide self-care:** Patients can have severe problems in washing or dressing or are unable to wash or dress
- **undertaking usual activities:** Patients can have severe problems in doing their usual activities or are unable to do their daily activities
- **experience of pain/discomfort:** Patients can have severe pain or discomfort
- **experience of anxiety/depression:** Patients can be severely anxious or depressed

Further details of impact upon patients:

IIMs can occur suddenly or gradually with muscle weakness, a skin rash and involve multiple organs. Patients complain of difficulty getting up from a chair, climbing stairs, lifting things, and combing hair. It is usually painless, pain can be significant in acute disease, skin ulceration, subcutaneous calcifications and from muscle tenderness. Some patients develop shortness of breath due to lung disease or ventilatory muscle weakness. Some suffer from the related complications of congestive heart failure or arrhythmias, have difficulty swallowing and gastrointestinal bleeding.

Patients often require walking devices and facilitating devices for hygiene activities. Aids to facilitate arising, gripping/opening and reaching are also commonly required.

Further details of impact upon carers:
Nearly half of patients depended on caregivers for errands and shopping, getting in and out of the car or housework or gardening. Patients require help with reaching objects, assistance with dressing and with rising. Help with walking, maintaining hygiene and eating is also sometimes required.

Considerations from review by Rare Disease Advisory Group

Not applicable.

Pharmaceutical considerations

This Clinical Commissioning Policy Proposition recommends abatacept for refractory idiopathic inflammatory myopathies in adults and children aged 2 years and over. This is an off-label use of the medicine. Abatacept is licensed in children 2 years of age and older for the treatment of polyarticular juvenile idiopathic arthritis (pJIA). Abatacept is excluded from tariff.

Considerations from review by National Programme of Care

The NPoC noted the significant impact on patients with IIMs which is the focus of this policy proposition. The proposition received the full support of the Internal Medicine NPoC Assurance Group on 17th September 2021. The NPoC noted the management of rare Rheumatological conditions are predominantly provided through Specialised Rheumatology adult and children's services. The proposal is cost saving overall as it reduces the need to use IVIg treatment which is the current treatment for IIM.